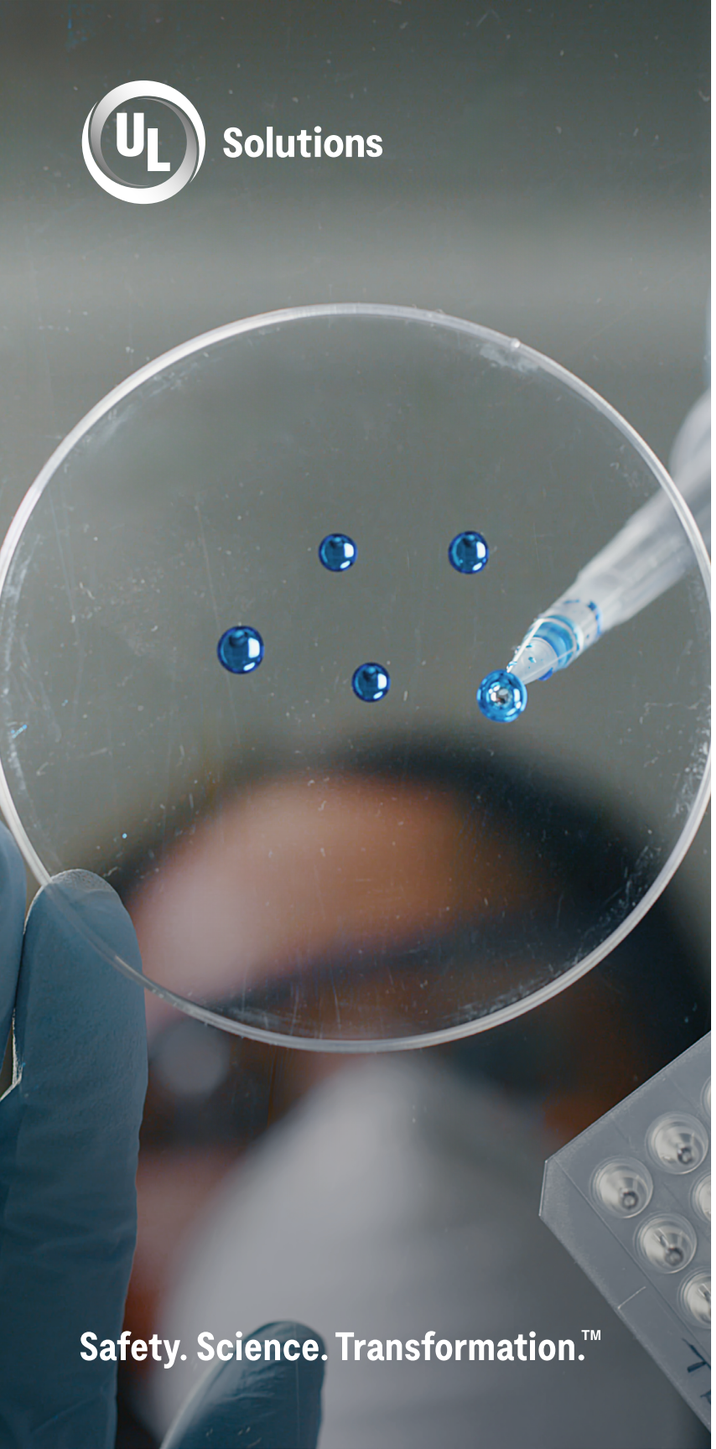

Biological Evaluation of Medical Devices ISO 10993-17: Main revisions for 2023

ISO 10993-17 was revised in September 2023 for the first time in approximately 20 years. Revised ISO 10993-17: The following are some of the new terms and concepts introduced in 2023:

The ISO 10993 series of standards primarily deals with biological evaluation of medical devices. ISO 10993-17 sets out requirements for this series with regard to the methods used to assess the toxicological risk of chemical substances identified in chemical characterization (ISO 10993-18).

New Terminology and Risk Management Processes

The 2023 edition of ISO 10993-17 introduces new terms and concepts such as toxicological screening limit (“TSL”), estimated exposure dose (maximum; EEDmax), and release kinetics. It also provides flowcharts outlining how to incorporate toxicological risk assessment frameworks into medical device risk management processes and toxicological risk assessment reports.

During the hazard identification process, toxicological information on chemicals (primary and secondary health effects) at the point of departure (POD), such as the No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effect Levels (LOAELs) for relevant endpoints, must be collected from multiple sources/databases. (Examples of sources/databases: Toxplanet, National Toxicology Program (NTP), Environmental Protection Agency (EPA) PubMed, Carcinogenic Potency Database (CPDB), Registry of Toxic Effects of Chemical Substances (RTECS), European Food Safety Authority (EFSA), European Chemicals Agency (ECHA), World Health Organization (WHO), etc.)

Source/database selection and search criteria must be documented and justified, and the reliability and quality of the data assessed and established. Information about chemical substances must be documented, including animal models, age, sex, route of administration, dose, frequency of administration, type of harm associated with specific doses, and toxic effects. When toxicity information on a chemical substance cannot be obtained, a read-across*1 assessment can be performed using a structurally similar chemical with appropriate toxicity information as a surrogate.

*1 Read-across is a method for filling data gaps for endpoints such as the toxicity of a substance for which predictions are to be made (a target substance) using data on a substance (source substance) that is similar to the target substance. (Reference: https://www.cerij.or.jp/service/10_risk_evaluation/QSAR_01.html#m2)

Toxicological Screening Limit—TSL

One of the key changes in the 2023 edition of ISO 10993-17 is the introduction of a new concept called the toxicological screening limit (TSL). TSL is the amount of cumulative exposure to a specified substance over a specified period of time that will not cause significant health effects. The unit used for TSL is µ/d. TSL can be used to assess whether the total amount of an identified substance is low enough not to cause genotoxicity, carcinogenicity, systemic toxicity (acute, subacute, subchronic, chronic, etc.), or reproductive or developmental toxicity. If the total amount of a chemical substance is below the TSL, there is no need to conduct a toxicological risk assessment. The main objective of implementing TSL is to reduce the burden on toxicologists and to focus toxicological risk assessment on potentially hazardous chemical components. TSL is applied to the total amount of a chemical that can be extracted or identified from an applicable medical device.

Additionally, there are some limitations to this TSL concept, as indicated below.

- If the hazard is irritating in nature
- If there are insufficiently identified chemical substances (unknowns) present
- For medical devices used in prolonged long-term contact with premature infants, newborns, and extremely young infants (<16 weeks)
- If a substance is part of a group of chemicals of concern
- For volatile organic compounds (VOCs) from gas-path medical devices

Moreover, TSL is not a substitute for the analytical evaluation threshold (AET) defined in ISO 10993-18:2020. TSL can be used to identify chemical substances requiring toxicological risk assessment and to assess their safety in extracts above the AET.

For tolerable intake (TI) calculations, select the most clinically relevant POD. This standard identifies quantitative levels of uncertainty for the oral route, duration of exposure, POD, data applicability, and uncertainties of quality. When using information on the oral route to derive information on parenteral intake, it is necessary to also take into account the uncertainty factor (UF) for the oral route as well as data on the internal circulation, absorption, and reactions of the chemical substance upon ingestion. For patient populations including preterm infants, neonates, and extremely young infants (<16 weeks), an additional uncertainty factor (UF) of 3 must be applied.

When specific toxicological information on a chemical substance is not available, a threshold of toxicological concern (TTC) approach is used. A TTC for mutagenicity/carcinogenicity can be selected based on the duration of exposure to the chemical. If toxicological data indicate that a chemical substance does not induce a genotoxic response, TTC (classification by Cramer Class) of non-carcinogenicity can be selected. This includes cases where mutagenicity data are negative or where at least two computational models, such as systems-based and statistical-based, give negative results.

Maximum Exposure—About EEDmax

Another new concept is EEDmax. EEDmax is the worst-case daily exposure to a chemical if it comes into contact with the body or is ingested. There are two approaches to ascertaining that information regarding EEDmax.

If information on the release kinetics of the chemical substance (which allows an estimate of the amount of substance released from the medical device over a certain period of time) is available
EEDmax can be determined based on the release kinetics of the chemical substance (identifying the highest quantity (release kinetics) per day (HQ r. k.)) as determined through release kinetics testing for each period.

When chemical release kinetics information is not available
The worst-case scenario is calculated by dividing the expected release amount (TQ: Total quantity) by the number of days of release (Rd: Release duration) for each period. In both situations, a scaling factor (the maximum quantity of medical equipment used in clinical practice) must be applied.

Evaluation taking release kinetics into account

For medical devices, it may make more sense to calculate the maximum daily exposure (EEDmax) at each time point during the exposure period (within a day, month, year, etc.) rather than the total amount of chemical substance released during the device's lifetime. The EEDmax approach can be used to capture exposure conditions that are more relevant to clinical use. The main advantage of EEDmax is that it allows evaluation of the potential of chemical substances specified in ISO 10993-1 to induce effects for a variety of contact time categories (acute, subacute, subchronic, or chronic toxicity).

The Margin of Safety (MoS) can be calculated by dividing the Tolerable Intake (TI) by EEDmax. Using this new concept, it is now possible to calculate MoS for multiple time periods: acute (1 day), subacute (2–30 days), subchronic (30–365 days), and chronic (365 days). If the MoS is higher than 1, the EEDmax of a chemical substance is not considered to pose a significant risk to human health if the values associated with MoS calculation are based on conservative information. However, if the MoS is less than 1, further consideration of toxicological risk is necessary. In accordance with ISO 10993-1 and ISO 14971, additional approaches will be considered to address toxicological risks.

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